Clinical and genetic profiles of grey matter heterotopia – report of 28 patients

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ICNC 2022
17th INTERNATIONAL CHILD NEUROLOGY CONGRESS
ANTALYA, TURKEY | OCTOBER 3-7, 2022

Background:

Heterotopia are rare brain malformations characterized by abnormal neuronal migration, with a wide heterogenous clinical and imagistic picture ranging from asymptomatic to severe epilepsy and developmental delay/intellectual disability (DD/ID). The etiology of BMs includs both genetic and enviromental factors.

We report on the results of a study on genetic etiology of heterotopia in a Romanian pediatric population.

Material and methods:

28 patients with heterotopia were included in this study. Phenotypic evaluation included a general clinical exam completed with neurologic, psychiatric, and psychological evaluations. Brain magnetic resonance imaging and electroencephalograms were also performed. Genetic investigations included array based comparative genomic hybridization, mutation screening of *DCX* and *FLNA* genes by Sanger sequencing, and whole genome sequencing.

Results

Brain MRI revealed subcortical band heterotopia in 2 patients, periventricular nodular heterotopia in 20 patients, and nodular subcortical heterotopia in 6 cases.

24 patients were referred for epilepsy with or without DD/ID.

Two genomic imbalances were identified, a duplication of 22q11.2 (Fig. 1) and a deletion of 7q35 which includes *CNTNAP2* gene (Fig. 2). A pathogenic frameshift mutation in *DCX* gene was identifed in a girl with band heterotopia.

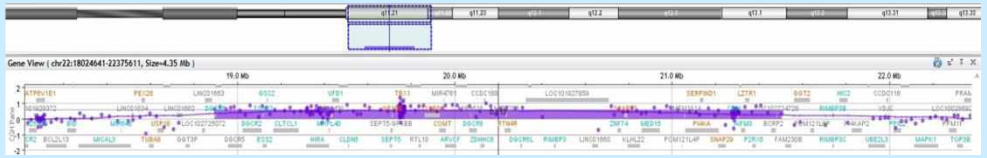

Figure 1. 22q11.2 duplication in a patient with left occipital nodular heterotopia, mild ID, epilepsy, and ADHD

Figure 2. 7q35 deletion in a patient with right frontal nodular heterotopia, epilepsy, ADHD, and normal intelligence

Discussions:

Our study brings new data on the clinical features and epilepsy phenotypes. Both genomic inbalances and gene mutations were detected in our patient group. Brain imaging and genetic studies were instrumental in the diagnostic and patient care algorithm. There are no previous reports of heterotopia associated with a similar 22q11.2 duplication. Homozygous or compound heterozygous mutations of *CNTNAP2* are associated with Cortical Dysplasia-Focal Epilepsy Syndrome # 610042. The contribution of these two CNVs to heterotopia pathogenesis worth further analysis.

Funding: This work was supported by grants of the Romanian National Authority for Scientific Research Innovation, CCCDI-UEFISCDI, Projects number 87/2019 and 88/2019, COFUND-ERANET E-RARE 3-HETER-OMICS-2, within PNCDI III.